UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,241	11/13/2001	Emil D. Kakkis	00800.0051.CNUS03	8479

7590 01/21/2004

NABEELA R. MC MILLIAN, PH.D,ESQ.
MARSHAL, GERSTEIN AND BORUN
233 SOUTH WACKER, 6300 SEARS TOWER
CHICAGO, IL 60606-6357

EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,241	KAKKIS, EMIL D.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *1-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-57 are currently pending and are present for examination. Claims 14-57 are now under consideration. Claims 1-13 remain withdrawn from consideration as being drawn to non-elected invention.

Applicants' amendments and arguments filed on 9-26-03, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 26 recites the phrase "reduces lysosomal storage". The metes and bounds of the above phrase are not clear to the Examiner specifically with respect to the term "reduces" in the context of the above claim. It is not clear to the Examiner as to what specifically is reduced in the lysosome. In other words, the treatment reduces lysosomal storage of what?

Examiner acknowledges the exhaustive response to the series of rejections under 35 U.S.C. 112, 2nd paragraph. However, the above rejection is maintained because applicant's arguments are not persuasive to overcome the above rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treatment using a greater than 99% pure, recombinant α-L-iduronidase enzyme with SEQ ID NO:2, does not reasonably provide enablement for such a method using mutants of the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 14-57 are so broad as to encompass a method of use of mutants of recombinant α L-iduronidase with SEQ ID NO:2. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the method of use of large number of mutants of SEQ ID NO:2 broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any,

are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides in the above method. The specification is limited to teaching use of SEQ ID NO:2 as the α-L-iduronidase and a method of its use in treating a human disorder but provides no guidance with regard to the making of mutants of SEQ ID NO:2 for such a use. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides for use in the method, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass the use of mutants of the enzyme with SEQ ID NO:2 because the specification does not establish:

(A) regions of the protein structure which may be modified without effecting activity; (B) the general tolerance of α-L-iduronidase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue in SEQ ID NO:2 with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use a mutant enzyme of SEQ ID NO:2 in the claimed method in a manner reasonably correlated with the scope of the claims broadly including mutants with an enormous number of amino acid modifications in SEQ ID NO:2. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of mutants having the desired biological characteristics for use in the claimed method is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicant has traversed the above rejection arguing at length, that given the instant specification those of skill in the art would be able to prepare and use fragments and mutants of SEQ ID NO:2 in the claimed treatment methods without undue experimentation and as such, applicant has fully enabled the scope of the methods claimed. Examiner respectfully disagrees that such an argument would be persuasive to overcome the above rejection. While applicant's amendments with respect to the use of fragments of SEQ ID NO:2 in the claimed method does overcome part of the previously alleged

enablement rejection, Examiner continues to maintain that amended claims are still not enabled for a method of treatment using mutants of SEQ ID NO:2 without undue experimentation as explained above. Applicant argues that while the method requires some routine experimentation such experimentation would not be undue. Applicant appears to have missed the point of the entire rejection. Applicant appears to argue at length as if the Examiner has rejected the claims as not enabled for making a preparation of more than 99% pure α L-iduronidase and its use in the treatment method. However, such is not the case. Examiner has rejected the claims as not enabled for a method which uses a mutant of SEQ ID NO:2. Without providing guidance for making mutants of SEQ ID NO:2, applicant proceeds to a method of using such mutants. The above method claims are not enabled because the method uses a mutant of SEQ ID NO:2 without a teaching of how to make said mutants. Reiterating what has already been explained in the above rejection, while methods to produce variants of a known sequence, such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing mutants for a method, as claimed by applicants requires that one of ordinary skill in the art know or be provided with guidance with regard to specific regions or specific amino acids in the enzyme's sequence that can be modified along with a method for the selection of polypeptides --from among the large number of variants that result from such a modification-- that have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of modifying each and every amino acid in the enzyme sequence as well as producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of

guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without effecting activity; (B) the general tolerance of α-L-iduronidase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue in SEQ ID NO:2 with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Hence the above rejection is maintained.

Claims 14-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 14-57 are directed to a method of treating using mutants of polypeptide with SEQ ID NO:2. Claims 14-57 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides derived from SEQ ID NO:2 that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:2 has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences derived from SEQ ID NO:2, including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable

genus including peptides which can have a wide variety of structure and function. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office action, applicant traverses the above rejection again with another exhaustive argument. In summary applicant appears to argue that the instant claims are drawn to methods of treatment and not compositions and the focus of the written description enquiry should be to look for "whatever is now claimed" and that the claims are drawn to methods of treatment and not protein sequences. Applicant also argues that the specification expressly states that those skilled in the art should be able to "design fragments of cDNA encoding biologically active fragments and mutants...." and therefore it is established that the specification contemplated method of treatment using fragments and mutants. Applicant also states that "it is inappropriate to judge the written description of the presently claimed methods based on a legal standard involving protein composition inventions". Examiner respectfully disagrees with all the above arguments of the applicant and reiterates that such arguments are not persuasive to overcome the rejection. Written description rules apply whether the claims are drawn to a method or composition. Examiner clearly understands the so called invention of the

applicant and has no confusion as to whether the claims are directed to a composition or a method. Claims in question are directed to a method of using a mutant enzyme whose structure has not been described in the specification.

Applicant argues that the situation in the instant case is identical to that provided in example 18 of the Guidelines. Examiner respectfully disagrees with such an argument that above two situations are identical because the claim in the example is not drawn a method of producing or using a mutant protein. Unlike the claim in example 18 of the Guidelines, instant claims are drawn to a method wherein a genus of polypeptides are used but whose structures have not been described. As discussed in the written description guidelines, the written description requirement may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing

only one species within the genus. In the instant case the genera of polypeptides to be used in the method of treating includes species which are widely variant in structure. As such, neither the description of the structure and function of just a single member such as SEQ ID NO:2 nor the disclosure of solely functional features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus. Therefore the above rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 14-57 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 6585971. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim, because the examined claim is either anticipated by, or would have been obvious over the reference claim. See, e.g., *In re Berg*, 140 F.3d 1428,46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi* 759 F.2d 887,225

USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 14-57 of the instant application and claims 1-30 of the reference patent are both directed to a method of treating using recombinant α-L-iduronidase (having an amino acid sequence SEQ ID NO:2). Among all the different fragments and muteins and purified enzyme claimed in the instant application a good number of the enzymes are identical to one another (i.e., the enzyme in the issued patent encompasses fragments and purified enzyme claimed in the instant claims). The portion of the specification (and the claims) in the reference patent that supports the recited amino acid sequence SEQ ID NO:2, includes several embodiments (fragments, purified enzyme) that would anticipate the fragments and purified enzyme claimed in claims 14-57. Claims of the instant application listed above cannot be considered patentably distinct over claims 1-30 of the reference patent when there is specifically recited embodiment that would anticipate mainly claims 1-30 of the instant application. Alternatively, claims 14-38 cannot be considered patentably distinct over claims 1-30 of the reference patent when there is specifically disclosed embodiment in the reference patent that supports claims 1-30 of that patent and falls within the scope of claims 14-38 herein because it would have been obvious to one having ordinary skill in the art to modify claims 1-30 of the reference by selecting a specifically disclosed embodiment that supports those claims i.e., muteins of recombinant α-L-iduronidase with SEQ ID NO:2. One of ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being a preferred embodiment within claims 1-30 of the reference patent.

In response to the previous Office action, applicant has requested that Examiner hold the above rejection in abeyance. However, the above rejection is maintained for reasons of record.

Conclusion

None of the claims are allowable.

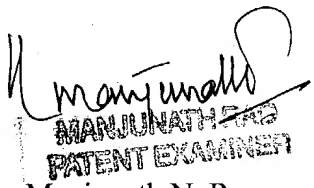
THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached between 7.30 a.m. to 4.00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.



Manjunath N. Rao
January 7, 2004